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UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Attorney Docket No.	SUR-008
First Named Inventor	Sawan
Title	Topical Dermal Antimicrobial Compositions, Methods for Generating Same, and Monitoring Methods Utilizing Same

APPLICATION ELEMENTS	ACCOMPANYING APPLICATION PARTS
ADDRESS TO: **Box Patent Application, Assistant Commissioner for Patents, Washington, D.C. 20231**	
1. ☐ Fee Transmittal Form	
2. ☒ Specification and Drawings [Total Pages 51] - Specification - (36 pages) - Claims - (10 pages) - Abstract - (1 page) - Sheets of Drawings - (4 sheets) ☐ Formal ☒ Informal	7. ☐ 37 CFR 3.73(b) Statement (when there is an assignee) ☐ Power of Attorney 8. ☐ English Translation Document *(if applicable)* 9. ☐ Information Disclosure Statement (IDS)/PTO-1449 ☐ Copies of IDS Citations
3. ☐ Oath or Declaration [Total Pages] a. ☐ Newly executed (original) b. ☐ Copy from a prior application (37 CFR 1.63(d)) *(for continuation/divisional with Box 17 completed)* ***[Note Box 4 below]***	10. ☐ Preliminary Amendment ☐ Drawings [Total Sheets] ☐ Letter to Official Draftsperson Including Drawings [Total Pages] 11. ☒ Return Receipt Postcard
4. ☐ Incorporation by Reference (usable if Box 3b is checked) The entire Disclosure of the prior application, from which a copy of the oath or declaration is supplied under Box 3b, is considered as being part of the disclosure of the accompanying application and is hereby incorporated by reference therein.	12. ☐ Small Entity Statement(s) ☐ Statements filed in prior application, (Status still proper and desired) 13. ☐ Certified Copy of Priority Document(s)
5. ☐ Microfiche Computer Program *(Appendix)*	14. ☐ Deletion of Inventor(s) Signed statement attached deleting inventor(s) named in the prior application.
6. ☐ Nucleotide and/or Amino Acid Sequence Submission ☐ Computer Readable Copy ☐ Paper Copy (identical to computer copy) ☐ Statement verifying identify of above copies	15. ☒ Patent Application Data Entry Form 16. ☒ Other: This application claims priority under 35 U.S.C. 119 to prior provisional application Serial Nos. 60/099,925 filed September 11, 1998 and 60/116,013 filed January 15, 1999.

17. ☐ **If a CONTINUING APPLICATION,** check appropriate box and supply the requisite information:
☐ Continuation ☐ Divisional ☐ Continuation-in-part (CIP) of prior application Serial No. _____.
Priority to the above application(s) is claimed under 35 U.S.C. 120.
Prior application information: Examiner: _____. Group/Art Unit: _____.

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Application Information

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Representative Information

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Continuity Information

This application claims priority to ::	Provisional Applications
>Application One ::	60/099,925
Filing Date ::	September 11, 1998 and
>>Application Two ::	60/116,013
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UTILITY PATENT APPLICATION
DOCKET NO.: SUR-008

TOPICAL DERMAL ANTIMICROBIAL COMPOSITIONS, METHODS FOR GENERATING SAME, AND MONITORING METHODS UTILIZING SAME

Related Application Data

This application claims priority to United States Serial No. 60/099,925, filed September 11, 1998, and United States Serial No. 60/116,013, filed January 15, 1999, the disclosures of which are herein incorporated by reference.

Field of the Invention

The present invention relates generally to topical antimicrobial compositions having initial and residual disinfectant activity. The invention also relates more specifically to topical dermal antiseptic compositions containing a self-preserving antimicrobial polymer that exhibit sanitizing properties when applied on skin, and form microbial barrier films in-situ that are moisture and sweat resistant, and provide "persistence" or extended duration residual antimicrobial efficacy in water contacting environments, and deodorizing action that is moisture and sweat resistant.

Background of the Invention

The constant threat of bacterial contamination and the associated repercussions on health have made antiseptic products such as antimicrobial creams, lotions, sprays, gels, foams and deodorants a ubiquitous part of personal hygiene. Antiseptic sanitizers are especially important in susceptible environments such as hospitals, healthcare facilities and food service areas in residential kitchens and in restaurants. Common antiseptic products that contain ethanol, isopropanol, triclosan, etc. provide sanitizing efficacy upon application. Such efficacy, however, is short lived, since such products are incapable of providing long lasting protection in terms of persistent residual antimicrobial action. This often results in recontamination of surfaces, requiring frequent reapplication of antiseptic. Relatively high concentrations of the active agent must be incorporated in these formulations in order to

obtain broad-spectrum activity. Such high concentrations or repeated reapplication often have undesirable side effects, particularly when the agent is applied to skin. These side effects can include, for example, skin irritation and dermal sensitization. These compounds can also contaminate food products and can be responsible for unpleasant tastes or odors and can be potentially harmful to consumers if ingested. Furthermore, presently available antiseptic formulations make it difficult, if not impossible, for employers to monitor individual compliance with sanitary procedures. Food service or healthcare workers who fail to adhere to proper hygiene and sanitary procedures can potentially transmit pathogenic bacteria to unsuspecting consumers or patients.

Dermal antiseptic formulations are generally categorized as surgical scrubs, preoperative skin preparations, healthcare personnel handwashes, food handler handwashes and general population handwashes. This categorization is based on efficacy of such products against pathogenic microorganisms relevant to the area of use. They contain either a single antimicrobial agent or a mixture of more than one agent that are considered "active ingredients". The type of active ingredients used in an antiseptic formulation is dependent on the category of its use. Formulations used as surgical scrubs and pre-operative skin preparations typically contain alcohol (ethanol, *n*-propanol or isopropanol), chlorhexidine gluconate, iodine, or povidone-iodine complex. Such agents have a number of limitations, such as skin dehydration causing dryness (in the case of alcohols), skin irritation and sensitization (in the case of chlorhexidine and iodine), and skin discoloration (in the case of iodine and its complexes). Alcohol and iodine based antiseptics do not exhibit residual antimicrobial activity or "persistence" that is a prerequisite characteristic for products in this category, due to their volatility. They must therefore be either be formulated with emollients to retard evaporation from the skin (for alcohols) or complexed to control their release (povidone-iodine). Furthermore, active ingredients for formulations used in other categories such as triclosan, triclorocarban and *para*-chloro-*meta*-xylenol (PCMX) are restricted by regulations for use as surgical scrubs.

Alcohol-based antiseptics for use in dermal applications such as surgical scrubs, preoperative skin preparations and antiseptic handwashes are well known and widely used because of their high effectiveness and the rapidity with which they kill microorganisms, as well as their non cytotoxicity. Alcohol containing formulations, containing 60-95% by volume of ethanol or isopropanol, are often used as surgical scrubs, in preoperative skin preparations, as healthcare personnel handwashes and antiseptic handwashes to disinfect hands, and for localized skin disinfection at the site of an invasive medical procedure. The efficacy of such compositions is short term, due to rapid evaporation of the alcohol, which is the antimicrobially active ingredient. Other limitations resulting from the use of such formulations include skin dryness and difficulty in application due to their low viscosity and watery nature. Their use in applications requiring sustained antimicrobial efficacy (persistence), such as surgical scrubs, is therefore limited by their high vapor pressure (which causes rapid evaporation upon application). Thus, when applied to skin, the rapid decrease in alcohol concentration limits the agent's contact time with microbes, especially bacteria, due to evaporative loss. U.S. Patent No. 5,288,486 discloses a method to decrease the evaporation rate of alcohol by addition of an alcohol soluble viscosifying agent to prolong its activity. Such compositions, however, are not capable of providing a film on skin that can continue to exhibit antimicrobial activity over extended periods, especially after contacting water or aqueous solutions. These compositions do not provide residual barrier properties precluding bacterial penetration of the barrier and subsequent contamination and proliferation on the underlying skin

There are other examples involving utilization of compositions that provide an antimicrobial barrier film on skin. Such compositions involve dispersing a water soluble, low molecular weight antimicrobial agent in a film-forming polymer matrix. U.S. Patent No. 5,417,968 discloses an antimicrobial barrier composition wherein an antimicrobial compound is mixed with a film-forming polymer that can form a barrier film on skin, and allows for elution of the antimicrobial compound to impart antimicrobial property to the film. U.S.

Patent No. 4,374,126 discloses a skin adherent polymeric film into which an antimicrobial compound is impregnated so as to provide antimicrobial action via diffusion. Antimicrobial action of resultant films is effected by elution of the antimicrobial agent from the matrix via dissolution or diffusion. Such barrier films do not provide the rapid disinfection that is required of a surgical scrub, nor are they capable of providing extended antimicrobial efficacy after contact with water or aqueous solutions. Antimicrobial compositions disclosed in the prior art are therefore incapable of providing rapid antiseptic action and persistent antimicrobial efficacy, especially upon contact with water or aqueous solutions, for example, after a handwash. Such formulations would have to be reapplied to prevent subsequent microbial contamination. This limitation requires frequent use of the antiseptic, especially in hospital, healthcare and food handling areas where bacterial contamination can result in serious consequences. Furthermore, because these formulations elute when exposed to aqueous solutions (*e.g.* sweat), they can penetrate the skin barrier, rendering them potentially skin irritating and sensitizing with prolonged or continuous use. Such compositions do not provide microbial barrier properties or antimicrobial polymers that continue to exhibit antimicrobial efficacy on skin after contacting water as when handwashing. In regulated environments such as the healthcare and food industries, there is also a need to develop means to monitor employees' compliance with hygiene and sanitary procedures involving the use of dermal antiseptics and hand sanitizers.

Thus, there is a need to develop new, non-irritating disinfecting formulations that can provide fast-acting, broad-spectrum, persistent antimicrobial activity on surfaces, e.g. skin, without reapplication, even after contacting water. There is a need for antiseptic formulations that are self-preserving, that is, for formulations that do not require the addition of a soluble, low molecular weight antimicrobial agent to inhibit bacterial growth on a polymeric film formed in-situ on a surface and resistant to water.

There is a need for dermal antiseptic formulations exhibiting persistent efficacy and microbial barrier properties using low levels of the antimicrobial agent, thus avoiding skin irritation or sensitization for the user. Additionally, there is a need for dermal antiseptic formulations whose presence on skin can be readily determined.

There is a need for efficient deodorants that are moisture and sweat resistant. Antimicrobial deodorant compositions reported in the prior art are either effective for short duration due to volatility of the active agent (*e.g.,* alcohol) or are dissolved in sweat and dispersed, thereby rendering them effective only for short periods. Such deodorants must therefore be formulated in combination with an antiperspirant agent for extended duration efficacy. Such agents may cause skin dryness, irritation and sensitization. It is therefore desirable to have deodorants that are sweat and moisture resistant that provide extended duration deodorizing activity without the use of an antiperspirant agent.

Summary of the Invention

It is an object of the present invention to provide a non-eluting topical antimicrobial composition which is capable of (i) providing immediate broad-spectrum antimicrobial disinfection and (ii) providing sustained or residual antimicrobial disinfecting action for extended periods after application, even after being contacted by water or other liquids. An additional object of the invention is to provide a composition that can bind non-leachably to a surface. A further object of the invention is to provide an antimicrobial material that does not release biocidal amounts of leachables into a contacting solution. Another object of the invention is to provide a substantially water-insoluble, self-preserving microbial barrier film that imparts "persistence" (residual antimicrobial action) for extended periods after application. An additional object of the invention is to provide deodorizing action of extended duration on skin even after exposure to moisture and sweat. Another object of the invention is to provide a topical antimicrobial composition which comprises an optical reporter, e.g., a fluorophore or an optical brightening agent that enables detection of the presence of the topical antimicrobial composition on skin surfaces by suitable detection devices such as irradiation by an ultraviolet, fluorescent, infrared, or visible light source.

A further object of the present invention is to provide methods for detecting the presence of antimicrobial compositions on skin surfaces by providing a topical antimicrobial composition that contains an optical reporter. An additional object of the present invention is to provide methods for monitoring a subject's compliance with sterile or sanitary procedures by providing an antimicrobial composition that contains a marker and subsequently exposing

the subject to a detector capable of detecting the presence of the marker on the subject in order to determine whether the subject applied the composition.

Another object of the present invention is to provide a non-eluting, self-preserving polymeric antimicrobial material that (i) forms a microbial barrier in-situ upon application to skin and (ii) is capable of inhibiting microbial growth and preventing microbes from growing through the barrier over extended periods to the surface of underlying skin. It is an object of the invention to render the self-preserving polymeric material substantially water-insoluble so as to make it non-eluting; that is, it does not dissolve, elute or leach into contacting aqueous solutions at bactericidal levels. This is accomplished by making it conducive to spontaneously associating with skin and bonding to it via electrostatic, ionic or covalent bonding.

It is also an object of the invention to render the self-preserving polymer further water-insoluble by reacting it with a hydrophobic organic compound. Such a modification renders the polymeric antimicrobial material substantially water-insoluble, thereby enabling it to efficiently associate with skin upon application.

Another object of the invention is to react the antimicrobial polymeric material with a covalent coupling agent so that the resulting adduct is capable of forming covalent chemical bonds with functionalities such as amino, sulfhydryl, or carboxylic acid groups. Such covalent bonding enables retention of the antimicrobial polymer upon its application to an appropriate surface. Thus, the antimicrobial polymer provides a non-leachable, non-eluting microbial barrier that is capable of rapid sanitation and persistent antimicrobial activity that is substantially undiminished even upon contacting water.

An additional object of the present invention is to provide a topical antimicrobial composition comprising a second antimicrobial component non-leachably dispersed in the self-preserving barrier-forming antimicrobial polymeric material such that the antimicrobial component is capable of enhancing the persistent antimicrobial efficacy of the latter by killing microorganisms on contact without leaching from the composition into the surrounding environment at levels toxic to microorganisms. Such antimicrobial compositions are capable

of providing residual antimicrobial activity on dermal surfaces even after repeated exposure to aqueous solutions and thus are particularly useful as dermal antiseptics and hand sanitizers.

Thus, the present invention discloses compositions for a dermal antiseptic that exhibits rapid antimicrobial action upon application to skin, and provides residual antimicrobial action (persistence) over extended time periods even upon contact with water. The scope of the present invention is not limited to alcohol-containing skin antiseptics, and can be extended to non-alcohol-containing formulations that contain antimicrobially active materials such as chlorhexidine, iodine, povidone-iodine complexes, triclosan, triclorocarban, para-chloro-meta-xylenol, etc., in aqueous or organic solvents to provide similar benefits.

More particularly, the topical compositions of the present invention comprise a solution or dispersion of a polymeric antimicrobial material and a metallic biocide in a carrier, that, when applied to a surface, forms a substantially water-insoluble coating or film in which the biocide is non-leachably bound, complexed, associated or dispersed. The polymeric material preferably comprises a polymer, copolymer or adduct which contains segments that, when the polymer forms a film on a surface, are capable of engaging microorganisms that come into contact with it. The biocide preferably is non-leachably attached to, complexed or associated with or dispersed within the film, but is capable of being preferentially transferred directly from the polymeric film to the contacting microorganism due to a higher affinity of the biocide for proteins within the microorganism.

In one aspect, the present invention relates to a topical antimicrobial composition comprising (i) an antimicrobial complex comprising an organic polycationic polymeric antimicrobial material and an antimicrobial metallic material wherein said metallic material is non-leachably bound to or associated with said organic polymeric antimicrobial material and (ii) a carrier, wherein the antimicrobial complex is dispersed within said carrier.

The organic material must possess two important properties: it must be capable of reversibly binding or complexing with the biocide, and must be capable of insinuating the biocide into the cell membrane of a microorganism in contact with it. The organic material preferably is capable of disrupting or interacting with the cell membrane surrounding the microorganism. Preferred organic materials are those which can be applied on a surface as

substantially water-insoluble films and which bind the biocide in such a manner as to permit transfer of the biocide into the microorganism without releasing the biocide (at biocidal levels) into the surrounding environment, e.g., into the air or into any liquid in contact with the coated surface. Preferred organic materials are polycationic polymeric antimicrobial materials such as biguanide polymers. Especially preferred biguanide polymers include poly(hexamethylenebiguanide), poly(hexamethylenebiguanide) hydrochloride, or derivatives thereof.

The biocide preferably is an antimicrobial metallic material that is toxic to microorganisms and is capable of complexing with or reversibly binding to the organic matrix material, thereby rendering the organic matrix substantially water-insoluble. The metallic biocide exhibits greater binding affinity to thiol functional groups in cellular proteins of microorganisms. When a microorganism contacts the polymeric organic material of the present invention, the polymer engages or disrupts at least the outer portion of the lipid bilayer of the microorganism's cell membrane sufficiently to permit insinuation of the metallic biocide into the microorganism, where cell proteins or proteins in the lipid bilayer compete effectively for the biocide due to favorable binding constants. Stated another way, the metallic material binds to or forms a complex with the organic material in which the association between the organic material and metallic material is sufficiently strong that the layer or film does not elute antimicrobial amounts of the metal into a contacting solution. However, the metallic material preferentially binds to thiol and amine functional groups in proteins in the microorganism and thus is transferred directly from the matrix to the microorganism. The antimicrobial metal is subsequently transported intracellularly and causes cell death. The result is a contact-killing delivery system that selectively transfers the metallic biocide to or into the microorganism's cell membrane upon contact, without elution or dissolution of the biocide into solution, thereby maintaining long term antimicrobial efficacy. Preferred metallic materials are silver or silver compounds and especially preferred compounds are silver iodide and silver nitrate.

The antimicrobial materials of the present invention are, therefore, molecularly designed to enable a matrix-bound biocide to retain high antimicrobial activity without elution

of any compounds into contacting solutions, carriers or other materials. The antimicrobial's activity stems from the sustained, cooperative biocidal action of its components. Selective transfer of one component from within the matrix directly to the microorganism upon contact is achieved via a "handoff" mechanism upon engagement and penetration of the microorganism's cell membrane by the organic material. The antimicrobial material, therefore, maintains long term efficacy without releasing toxic elutables into the surrounding environment. Components that can be used in the present invention to provide cooperative biocidal action can include both metallic and non metallic biocides.

The invention comprises topical compositions for immediate sanitation of a surface, such as skin, providing long-term residual antimicrobial efficacy or "persistence" over extended duration, even after being contacted with water under conditions simulating a hand rinse. In one embodiment, the formulation is a topical composition comprising a solution, dispersion or suspension of the organic polymeric antimicrobial material and the biocidal material in a suitable carrier. The composition need not be a homogeneous solution. If desired, stabilizing agents such as suspending agents or surface active agents may be included. The topical composition may also include an optical reporter, e.g., a fluorophore or an optical brightening agent that enables detection of the presence of the topical composition (e.g. the microbial barrier formed on skin) by use of suitable detection devices, such as irradiation by an ultraviolet, fluorescent, infrared, or visible light source.

The present invention discloses a method to enhance the activity of dermal antiseptic formulations that overcome the limitations of formulations known in the prior art and can be used in all of the above-mentioned categories of dermal antiseptics and disinfectants, since they confer on such formulations antimicrobial persistence that remains unaffected even after loss of active ingredients in the antiseptic by evaporation or dissolution by water contact. The antimicrobial materials of the present invention may be used to enhance the efficacy of commercial biocidal compositions containing active agents such as alcohol (ethanol and n-isopropanol), chlorhexidine (Hibistat™ and Hibiclens™) or povidone-iodide complex (Betadine™), and enable such formulations to exhibit persistent antimicrobial efficacy even

upon being contacted with water. Furthermore, the compositions of the present invention provide such antimicrobial activity without producing skin irritation or cytotoxicity.

The limitations in the prior known methods and compositions are overcome by the present invention which relates to the addition of a self-preserving film-forming polymeric antimicrobial agent that enhances the efficacy of alcohol-containing formulations and provides residual antimicrobial efficacy or persistence after alcohol evaporation, thereby allowing more efficient use of alcohols as skin disinfectants or antiseptics for applications such as surgical scrubs and pre-operative skin preparations where persistence is a necessary attribute. Additionally, the present invention relates to the in-situ formation of a microbial barrier or film on skin upon its application. This microbial barrier or film is self-preserving; it kills contacting microorganisms and prevents them from growing through or penetrating the barrier to underlying skin.

Thus, in one aspect, the present invention relates to methods for extending the duration of efficacy of a dermal antiseptic formulation by providing a dermal antiseptic formulation and mixing in a polycationic antimicrobial material, such that the antimicrobial material is capable of forming a self-preserving antimicrobial barrier upon application of the formulation to skin, wherein the barrier inhibits microorganism growth, thereby enhancing the antimicrobial efficacy of the antiseptic formulation by imparting residual antimicrobial activity that is persistent.

In another aspect, the present invention relates to compositions comprising a dermal antiseptic formulation and an organic, polycationic, antimicrobial polymer that binds to skin upon application. In one embodiment, the formulation spontaneously binds to skin upon application, forming a self-preserving antimicrobial barrier that provides persistent antimicrobial activity.

The present invention also relates to methods for detecting the presence of antimicrobial compositions on a surface by providing on the surface an antimicrobial composition comprising (i) an antimicrobial complex comprising a polycationic polymer and an antimicrobial metallic material, (ii) a carrier, and (iii) a marker, and exposing the surface to a detector capable of detecting the presence of the marker on the surface. The present invention further provides methods for monitoring a subject's compliance with sterile

procedures, these methods comprising providing to the subject an antimicrobial composition comprising (i) an antimicrobial complex comprising a polycationic polymer and an antimicrobial metallic material, (ii) a carrier, and (iii) a marker; and subsequently exposing the subject to a detector capable of detecting the presence of the marker on the subject.

These and other objects, features and advantages of the present invention will be better understood from the following description when read in conjunction with the accompanying drawings and examples.

Brief Description of the Drawings

Figure 1A is a schematic graphic illustration of the polymer/biocide complex of the present invention, forming a film on the surface;

Figure 1B is a schematic graphic illustration of the contact-killing ability of the film-forming matrix/biocide complex of the present invention upon contact of the film with microorganisms, wherein the polymer chains engage and disrupt the microorganism cell membrane; and

Figure 1C is a schematic graphic illustration of the penetration of the cell membrane and transfer of the biocide from the network to proteins in the microorganism, causing cell death.

Figure 2 is a bar graph of the number of colony forming units elutable from a hand after treatment with a surgical scrub protocol, relative to a control baseline determination. The surgical scrub comprises an adduct of polyhexamethylenebiguanide hydrochloride with methylene-bis-N,N-diglycidylaniline. The scale is logarithmic, and the error bars indicate the 95% confidence interval.

Figure 3 is a bar graph of the number of colony forming units elutable from a hand after treatment with a surgical scrub protocol, relative to a control baseline determination. The surgical scrub comprises silver complexed to an adduct of polyhexamethylenebiguanide hydrochloride with methylene-bis-N,N-diglycidylaniline. The scale is logarithmic, and the error bars indicate the 95% confidence interval.

Detailed Description

The topical antimicrobial compositions of the present invention can be applied directly to the skin's surface to disinfect the area of application upon contact. The antimicrobial compositions also provide residual activity to kill microorganisms contacting the area of application subsequent to the initial treatment.

The term "microorganism" as used herein includes pathogenic organisms and infective agents, including bacteria, viruses, blue-green algae, fungi, yeast, mycoplasmids, protozoa, parasites and algae.

The term "biocidal" as used herein means bactericidal or bacteriostatic. The term "bactericidal" as used herein means the killing of microorganisms. The term "bacteriostatic" as used herein means inhibiting the growth of microorganisms, which can be reversible under certain conditions.

As used herein, the terms "non-eluting", "non-leachable" and "substantially non-leachable" mean that bioactive components in the disinfecting compositions do not dissolve, elute, leach or otherwise provide species into a liquid environment in contact with the compositions at levels that would result in solution disinfection, that is, in antimicrobially effective amounts. Preferably, this threshold is below the minimum solution inhibitory concentrations (MIC) of such components to cause the contacting solution to be biocidal.

As used herein, the terms, "sanitizer" and "antiseptic" refer to those mixtures that are applied to skin for the purpose of killing bacteria and microorganisms on the skin. Such mixtures may be used as surgical scrub hand washes, patient pre-operative skin preparations, and as healthcare personnel, food handler and general population hand washes. Other uses will become apparent to those skilled in the art and are intended to be within the scope of this invention.

The phrase "self-preserving antimicrobial barrier or film" as used herein refers to any antimicrobial polymeric compound that is capable of forming a barrier or film on the surface of a substrate such as skin, and inhibits the proliferation of microorganisms on said film, and prevents them from growing through to underlying skin. The phrase "residual antimicrobial

activity" as used herein refers to the activity of any chemical compound that is capable of forming a residue on a substrate surface and, upon its application, is capable of providing either bacteriostatic or bactericidal activity. When present in a dermal antiseptic or disinfectant formulation containing other active antimicrobial agents, the residue obtained from such agent is capable of sanitizing (bactericidal action) or acting as a preservative to prevent organism growth (bacteriostatic action). The term "persistence" as used herein refers to the ability of an antimicrobial material to inhibit bacterial regrowth on skin for an extended period of time after the initial antiseptic action caused by application of the antimicrobial formulation.

Organic materials useful in the present invention comprise antimicrobial materials which are capable of: (1) adhering to and/or forming a layer or coating on a surface such as skin, (2) reversibly binding to or complexing with a biocide to prevent its elution or dissolution, and (3) insinuating the biocide into the cell membrane of contacting microorganisms. A preferred class of materials are those having the aforementioned properties, which are capable of being immobilized on a surface and which preferentially bind to biocidal materials (especially metallic biocides) in such a manner so as to permit release of the biocide to the microorganism, but not to the contacting environment. More preferred is the class of organic materials that can attach to a surface by forming covalent chemical bonds with reactive moieties such as amino or carboxylic acid groups. Most preferred is the class of organic materials having antimicrobial properties: materials that, when applied as a coating, can dissolve into, adhere to, disrupt or penetrate the lipid bilayer membrane of a microorganism in contact with the barrier film. In a preferred embodiment, the organic material is a polymer containing segments which, when the polymer forms a coating on a surface, are capable of engaging microorganisms which come into contact with the coating. By "engaging" it is meant that the coating can attach and temporarily immobilize a microorganism in contact with it. The barrier film can dissolve into, or adhere to, and penetrate at least the outer portion of the lipid bilayer membrane of a microorganism. For this purpose, surface active agents, such as cationic compounds, polycationic compounds, anionic compounds, polyanionic compounds, non-ionic compounds, polyanionic compounds or zwitterionic compounds may be used. These compounds include, for example, biguanide

polymers, or polymers having side chains containing biguanide moieties or other cationic functional groups, such as benzalkonium groups or quarternium groups (e.g., quarternary amine groups). The polymer backbone may be any polymer capable of forming a coating on a substrate. It is understood that the term "polymer" as used herein includes any organic material comprising three or more repeating units, and includes oligomers, polymers, copolymers, terpolymers, etc. The polymer backbone may be a polysilane or polyethylene polymer, for example. Organic materials which currently are most preferred for use in the invention are polymeric biguanide compounds. When applied to a substrate, these polymers form a barrier film that can engage and disrupt a microorganism as shown in Figure 1.

Polymeric materials useful in the present invention include polymers containing benzalkoniumchloride or its derivatives, α-4-[1-tris(2-hydroxyethyl) ammonium-2-butenyl] poly[l-dimethylammonium-2-butenyl]-ω -tris(2-hydroxyethyl) ammonium chloride. Preferred polymeric compounds include polymeric biguanides and their salts of the general formula:

$$Y_1\text{-}[\text{-NH-C(=NH}^+\text{Z}^-\text{)-NH-C(=NH}^+\text{Z}^-\text{)-NH-X-}]_n\text{-}Y_2$$

or their water soluble salts, where X is any aliphatic, cycloaliphatic, aromatic, substituted aliphatic, substituted aromatic, heteroaliphatic, heterocyclic, or heteroaromatic compound, or a mixture of any of these, and Y_1 and Y_2 are any aliphatic, cycloaliphatic, aromatic, substituted aliphatic, substituted aromatic, heteroaliphatic, heterocyclic, or heteroaromatic compound, or a mixture of any of these, where n is an integer equal to or greater than 1, and wherein Z is an anion such as Cl^- or OH^-. In a preferred embodiment, the polymeric material is capable of adsorbing to a surface via electrostatic interaction, ionic interaction, or "hydrophobic forces". In another preferred embodiment, the polymeric material can bond covalently with a surface. Currently, the most preferred polymeric compound is polyhexamethylenebiguanide hydrochloride (available from Avecia, Inc. of Wilmington, DE as a 20% aqueous solution under the trade name COSMOCIL-CQ™). Similarly preferred polymeric compounds include poly(hexamethylenebiguanide) hydrochloride, poly(hexamethylenebiguanide) gluconate, or poly(hexamethylenebiguanide) derivatives.

In another preferred embodiment, the organic polymeric material may be further reacted with a substantially water-insoluble organic compound or "hydrophobic agent" to form a substantially water-insoluble adduct that is capable of forming a barrier or film *in situ* upon application to skin that is impervious to contact with water or aqueous solutions. As used herein, "substantially water-insoluble" means that bioactive components in the disinfecting compositions do not dissolve, elute, leach or otherwise provide species into a liquid environment in contact with the compositions at levels that would result in solution disinfection, that is, in antimicrobially effective amounts. Preferably, this threshold is below the minimum solution inhibitory concentrations (MIC) of such components to cause the contacting solution to be biocidal. This adduct, when added to a dermal antiseptic formulation or other carrier, confers on it a residual antimicrobial activity or persistence for extended periods of time in water-contacting (aqueous) environments. In a preferred embodiment, the organic material is a polymeric polycationic polymer, which is chemically reacted with a hydrophobic agent to form an adduct. The adduct that includes the hydrophobic agent exhibits greater water-insolubility, thus adhering more strongly to a surface such as skin than does the polycationic polymer alone. Hydrophobic agents which can be used in the present invention are organic compounds which are substantially water-insoluble and which can react with the polycationic material to form an adduct. Suitable hydrophobic agents include, for example, organic compounds containing a multifunctional groups such as a carbodiimide, isocyanate, isothiocyanate, succimidyl ester, epoxide, carboxylic acid, acid chloride, acid halide, acid anhydride, succimidyl ether, aldehyde, ketone, alkyl methane sulfonate, alkyl trifluoromethane sulfonate, alkyl paratoluene methanesulfonate, alkyl halide and organic multifunctional epoxide. In a currently preferred embodiment, a polyhexamethylene biguanide polymer is reacted with an epoxide, such as methylene-bis-N,N-diglycidylaniline, bisphenol-A-epichlorohydrin, or N,N-diglycidyl-4-glycidyloxyaniline. The degree of hydrophobicity of the resulting adduct can be adjusted by choice of the hydrophobic agent. The organic material can be polymeric or non-polymeric, and the resulting adduct may be capable of forming a coherent film.

In another preferred embodiment, the organic polymeric material comprises a chemical group that is capable of forming a covalent bond with a functional group on a

substrate. Suitable functional groups on the substrate might include, for example, an amino group, a carboxylic acid group, or a sulfhydryl group. Such a functional group could be found, for example, on a proteinaceous substrate or a substrate comprising a peptide. Appropriate substrates therefore include, for example, proteins, such as collagen, or living tissue, such as skin. In one embodiment, the substrate comprises a reactive chemical group such as a carbodiimide, isocyanate, isothiocyanate, succimidyl ester, epoxide, carboxylic acid, acid chloride, acid halide, acid anhydride, succimidyl ether, aldehyde, ketone, alkyl methane sulfonate, alkyl trifluoromethane sulfonate, alkyl paratoluene methanesulfonate, alkyl halide or an organic multifunctional epoxide. In another embodiment, the polymeric material comprises a reactive chemical group such as a carbodiimide, isocyanate, isothiocyanate, succimidyl ester, epoxide, carboxylic acid, acid chloride, acid halide, acid anhydride, succimidyl ether, aldehyde, ketone, alkyl methane sulfonate, alkyl trifluoromethane sulfonate, alkyl paratoluene methanesulfonate, alkyl halide, amino, sulfhydryl, or an organic multifunctional epoxide. Preferably, the covalent bond between the polymer and the substrate occurs at room temperature, *i.e.* at about twenty to twenty-five degrees Celsius, and occurs spontaneously. Thus, when the composition is applied to a suitable substrate, such as skin, it spontaneously forms one or more covalent bonds with the substrate, leaving an adherent residue conferring antimicrobial activity that is persistent, even after repeated exposure to aqueous solutions.

In another preferred embodiment, the organic polymeric material is chemically reacted with a coupling agent to form an adduct with compounds containing functionalities that are capable of further reacting with and forming covalent chemical bonds with functional groups (e.g. alkyl, ketone, aldehyde, amide, amino, carboxylic acid, sulfhydryl, etc.) upon application to a surface comprising one or more of these groups. Such covalent coupling to skin collagen, for example, results in a permanent immobilization of the polymeric antimicrobial material as a film or barrier that can impart immediate antiseptic sanitizing action followed by residual activity that is bactericidal (sanitizing) and/or bacteriostatic (peristence). Suitable coupling agents include compounds with carbodiimide, isocyanate, isothiocyanate, succinimidyl ester, epoxide, carboxylic acid, acid chloride, acid halide, acid anhydride, succimidyl ether, aldehyde, ketone, sulfonyl chloride, alkyl methane sulfonate,

alkyl trifluoromethane sulfonate, alkyl paratoluene methane sulfonates and alkyl halide. In a most preferred embodiment, the coupling agent is 1-[3-(Dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDCI).

Thus, in one preferred embodiment, the antimicrobial composition binds non-leachably to a surface by virtue of hydrophobic-hydrophobic interactions. In another embodiment, the antimicrobial composition binds non-leachably to a surface by virtue of electrostatic interactions. In another embodiment, the antimicrobial composition binds non-leachably by virtue of one or more covalent bonds formed between the composition and the surface. These embodiments are not exclusive: the binding of the antimicrobial composition to the surface could be stabilized by any combination of the above elements. In a preferred embodiment, one or more of these interactions occurs rapidly following application of the embodiment a surface. In a particularly preferred embodiment, these interactions can form at approximately room temperature, *i.e.* at about twenty to twenty-five degrees Celsius. In another preferred embodiment, these interactions can form when the composition is applied to skin collagen or to living skin. Preferably, these interactions can form in the presence of an antiseptic selected from the group consisting of ethanol, isopropyl alcohol, chlorhexidine gluconate, iodine, iodine-polyvinylpyrrolidone complex, triclosan, triclorocarban, benzalkonium chloride, and para-chloro-meta-xylenol. More preferably, these interactions can also form in the presence of a thickener, emollient, humectant, skin moisturizing agent or surfactant.

The polymeric antimicrobial material is preferably formulated in a topical composition that includes a second biocidal agent. This second agent comprises any antimicrobial material that is capable of non-leachably binding to, interacting with or complexing with the polymeric material, but which, when placed in contact with the microorganism, preferentially transfers to the microorganism. For this purpose, antimicrobial metallic materials which bind to cellular proteins of microorganisms and which are toxic to microorganisms are preferred. The metallic material can be a metal, metal salt, metal complex, metal alloy or mixture thereof. Metallic materials that are bactericidal or bacteriostatic and are substantially water-insoluble or can be rendered substantially water-insoluble are preferred. By a metallic material that is

bacteriostatic or bactericidal is meant a metallic material that is bacteriostatic to a microorganism, or that is bactericidal to a microorganism, or that is bactericidal to certain microorganisms and bacteriostatic to other microorganisms. Examples of such metals include, e.g., silver, zinc, cadmium, lead, mercury, antimony, gold, aluminum, copper, platinum and palladium, their oxides, salts, complexes and alloys, and mixtures of these. The appropriate metallic material is chosen based upon the ultimate use of the composition. The currently preferred metallic materials are silver compounds. In a currently preferred embodiment, a silver halide is used, most preferably, silver iodide. In another preferred embodiment silver nitrate is used which is converted into a substantially water-insoluble silver halide by subsequent chemical reaction with an alkali halide. Most preferably, silver nitrate is converted in-situ to silver iodide by reacting it with sodium or potassium iodide.

In a preferred embodiment, when the dermal antiseptic composition is applied to skin, the polymeric antimicrobial material forms a water- insoluble, non-leachable barrier or film wherein the bioactive functionalities are rendered capable of interacting with, but not diffusing into the bacterial cell membranes of microorganisms contacting it. This phenomenon can be understood by referring to Figure 1, which is a schematic graphic illustration of a preferred embodiment of the present invention in which the organic material is a polymeric biguanide that is rendered substantially water-insoluble by forming a complex with a water insoluble metallic material such as a silver halide, preferably silver iodide. Figure 1A show the polymer barrier film with functionalities capable of bacterial cell wall interactions projecting into the ambient environment, with the silver salt being present both in the complexed form and as entrapped sub-micron particles (as reservoirs). Without wishing to be bound by any theory, it is proposed that when a microorganism contacts the barrier film, the bioactive bisguanidine functionalities disrupt the lipid bilayer constituting the organism's cell membrane, thereby facilitating transfer of silver into the interior of the microorganism or to proteins within the cell membrane. Silver has a greater binding affinity for functionalities in cell membrane proteins than for the polymeric barrier film, and therefore is transferred to the microorganism. The silver is then transported intracellularly wherein it causes protein denaturation and inhibition of DNA synthesis, resulting in cell death. Specifically, it is

known that the silver forms complexes with the sulfhydryl and amino groups of the cellular proteins.

In this embodiment, the silver salt is complexed with the self-preserving antimicrobial polymeric material such that the silver is substantially non-leachable into the surrounding environment; neither the silver compound nor silver ions leach from the microbial barrier formed in-situ by the self-preserving polymer even in water contacting environments. The standard Kirby-Bauer zone of inhibition test using test substrates that contain disinfecting composition substantiates this. The absence of a zone in such tests indicates that bioactive components from the composition do not dissolve, elute, leach or provide species in the contacting medium at levels necessary to cause death. Again, not wishing to be bound by theory, it is believed that the silver salt forms complexes with functional groups in the self-preserving antimicrobial polymer, and that the resulting microbial barrier formed on skin containing complexed silver resists leaching into ambient liquids or other materials contacting it (e.g. water, and aqueous solutions including common cleaning liquids).

In a currently preferred embodiment, the polymeric material is poly(hexamethylene-biguanide) hydrochloride (PHMB.HCl). The preferred silver salt is a silver halide, most preferably silver iodide, or silver nitrate, which is readily converted to a silver halide, most preferably silver iodide. The silver halide complexed to PHMB.HCl provides a water-insoluble material that, when formulated in a topical composition, forms a self-preserving microbial barrier that provides antimicrobial efficacy over extended duration even in water-contacting environments. In another embodiment, the self-preserving antimicrobial polymeric material is rendered water-insoluble by chemically coupling it with a hydrophobic agent such as methylene-bis-N,N-diglycidylaniline (MBDGA) (commercially marketed as Araldite MY-720 by Ciba Giegy). The adduct is made by combining a solution of poly(hexamethylenebiguanide) with a solution of the hydrophobic agent, and reacting the mixture under conditions sufficient to form a PHMB-MBDGA adduct. The ratio of PHMB to MBDGA preferably is in the range of from about 1:1 to 3:1 by weight. The concentration of the resulting adduct resin preferably is in the range of from about 0.5 to about 20% by weight. A biocidal metallic material, preferably silver iodide, is added to the adduct solution to form

the antimicrobial complex. Silver solutions having a concentration of from about 0.005 to about 0.5% can be used for this step. Silver iodide is currently the most preferred form of the biocidal metallic material. It is added either to the adduct solution as such or obtained by adding silver nitrate to the adduct solution and converting it to silver iodide by addition of an alkali metal iodide such as sodium or potassium iodide. The silver iodide forms reservoirs in the matrix, and becomes attached to the tentacles. We have discovered that silver iodide has sufficient affinity for the PHMB polymer that it forms an insoluble complex that will not leach into ambient solutions or other materials in contact with the material, even at elevated temperatures. Silver has greater binding affinity for sulfhydryl groups in the bacterial cell membrane than for the PHMB-MBDGA matrix, and is therefore preferentially transferred from the coating to contacting microorganisms. The silver accumulates to toxic levels in the microorganism and kills it. The silver iodide reservoirs within the matrix replenish the silver iodide on the tentacles lost to the microorganism by reestablishing the equilibrium for formation of the complex

$$(AgI + PHMB \rightleftharpoons [PHMBAgI]).$$

Carriers useful in the present invention include any of generally known creams, lotions, powders, deodorants, sprays, gels, waxes, oils, or ointments, and may include emollients, thickeners, humectants, skin moisturizing agents and surfactants suitable for contact with skin surfaces. In one preferred embodiment, the cream lotion carrier is SoftGuard protective hand cream lotion (Stahmer Weston Scientific, Portsmouth, NH).

In one embodiment the carrier of the present invention is a dermal antiseptic formulation. Dermal antiseptic formulations suitable for use in the present invention are well-known to those skilled in the art. Such formulations include, but are in no way limited to, formulations comprising alcohols, chlorhexidine gluconate, iodine, iodine-polyvinylpyrrolidone complex, triclosan, triclorocarban and *para*-chloro-*meta*-xylenol. Currently preferred antiseptic formulations comprise water-soluble alcohols selected from the group consisting of ethyl alcohol, *n*-propyl alcohol, and isopropyl alcohol. In a preferred embodiment, the alcohol-based skin disinfectant or antiseptic comprises about 30 to about 95%, based on total formulation weight, of a water-soluble alcohol. Suitable dermal

antiseptic formulations could comprise, for example, surgical scrubs, pre-operative skin preparations, healthcare personnel handwashes, antiseptic handwashes, antimicrobial soaps, antimicrobial creams, antimicrobial hand sanitizers, antimicrobial deodorants, antimicrobial lotions, antimicrobial gels or other embodiments.

The topical compositions of the present invention are prepared by mixing, dispersing or blending the antimicrobial complexes with the carrier. It is preferable, but not necessary, to thoroughly blend the antimicrobial complex with the carrier to form a homogeneous mixture. The final concentration of the antimicrobial complex in the topical composition may vary depending on the intended use and particular formulation of the ultimate topical composition, as will be appreciated by those of ordinary skill in the art. The final concentration of the organic polycationic material may range from 0.5% to 50% by weight. Concentrations of the metallic material may range from 0.05% to 5% by weight.

The topical antimicrobial compositions of the present invention can also include an optical reporter, e.g., a fluorophore or an optical brightening agent that enables detection of the presence of the topical antimicrobial composition by use of suitable detection devices, such as irradiation by an ultraviolet, fluorescent, infrared, or visible light source. A preferred optical reporter is fluorescent brightener 28 (UVTex-OB, Ciba Specialty Chemicals Corp., Tarrytown, NY). Another preferred optical reporter is Tinopal SFP. When treated skin is examined under light (UV radiation at 365 nm), these optical reporters fluoresce, thereby confirming the presence of the antimicrobial composition. The optical reporter may be blended into the topical antimicrobial composition to a final concentration in the range of 0.05% to 5% by weight, and most preferably around 0.15% by weight.

Methods of the present invention relate to detection of the presence of the antimicrobial composition by first providing the topical antimicrobial composition plus optical reporter as described above, then exposing the surface of interest to a detector capable of detecting the presence of the optical reporter. These methods can be utilized as part of a coherent sanitary program to monitor a subject's compliance with sterile procedures using methods that comprise providing a subject with the topical antimicrobial compositions

including optical reporter of the present invention, and subsequently exposing the subject to a detector capable of detecting the presence of the optical reporter on the subject.

Additional methods of the present invention relate to enhancing and extending the duration of efficacy of a dermal antiseptic formulation by adding to the dermal antiseptic formulations described above a polycationic antimicrobial material as described above capable of forming a self-preserving antimicrobial film upon application to skin. The antimicrobial efficacy of the formulation is thus enhanced by the residual antimicrobial activity of the polycationic antimicrobial material. The polycationic antimicrobial material may comprise a metallic biocide as described above.

The invention is further illustrated by the following examples, which are not intended to be limiting in any way.

Example 1

Preparation of Surfacine® antimicrobial composition

Surfacine® antimicrobial composition was prepared according to the methods described in U.S. Application Serial Nos. 08/663,269 and 08/736,823, the entire disclosures of which are incorporated by reference herein. The final concentrations of the components in the antimicrobial composition are as follows:

PHMB-Araldite MY-720 adduct (2:1 w/w, pH 5.0±0. 1)	6.7%
Silver iodide	0.8%
Potassium iodide	1.2%
Sodium dodecyl sulfate	3.7%
N-methyl-2-pirrolidinone (NMP)	3.7%
Ethanol reagent	55.1%
Water	14.9%
Acetonitrile	13.8%

Example 2

Preparation of Antimicrobial Cream

SoftGuard protective hand cream lotion (Stahmer Weston Scientific, Portsmouth, NH) was used as the antimicrobial cream formulation base. SoftGuard protective cream is designed to eliminate latex glove irritation. The cream contains the following ingredients:

water, sorbitol, 1-hexadecanol, dimethicone, glyceryl monosteatate, lanolin, zinc oxide, sodium lauryl sulfate, methylparaben, propylparaben, quatornium- 15.

Surfacine® antimicrobial composition prepared as described in Example 1 and containing silver iodide, PHMB-Araldite MY-720 adduct and ethanol as the active ingredients was introduced into the cream base to give it antimicrobial properties. Specifically, 600 g of SoftGuard base was blended with 134.5 g of Surfacine antimicrobial formulation into a homogeneous mixture. The resulting antimicrobial cream ("AMC-1") had the following active ingredient content:

PHMB-Araldite MY-720 adduct	1.23%
Silver iodide	0.15%
Ethanol reagent	10.10%

Example 3

Preparation of Antimicrobial Cream with Optical Reporter

Antimicrobial cream as prepared in Example 2 was used and Fluorescent brightener 28 (FB-28) was added as an optical reporter in the antimicrobial cream formulation. Specifically, 0.20 g of FB-28 was mixed with 2 g of glycerol and 2 g of NMP to get a viscous paste. The paste was blended with 40 g of AMC- I formulation, then combined with additional 100 g of AMC-1 and homogenized in a blender.

The resulting antimicrobial cream with optical reporter ("AMC-2") consisted of:

AMC-1 (cream base)	97.08%
Glycerol	1.39%
NMP	1.39%
UVTex-OB	0.14%

Example 4

Initial Efficacy of Antimicrobial Hand Cream

Antimicrobial hand cream samples were tested to determine their efficacy at varied time points. The creams were tested for activity by incubation of the sample with several robust organisms (i.e., *Staphylococcus epidermis*-ATCC #12228, *Escherichia coli* 0157:H7-ATCC #43895, and *Pseudomonas aeruginosa*-ATCC #9027). If a three log or greater

decrease in the number of bacteria was detected as compared to the control, the cream was considered to be antimicrobial.

A.) Inoculum Preparation.

A well-isolated colony from a monoculture grown on Tryptic Soy Agar (TSA) was used to inoculate a 10 mL tube of Tryptic Soy Broth (TSB). The tube was then incubated for 18 hours +/- 2 hours, at 37°C. (The 18 hour culture contained ~ 10^9 cfu/mL.)

B.) Inoculum Enumeration.

A series of seven 1:10 dilutions in PBS of the 1 X 10^9 cfu/mL inoculum were performed and the 3 least diluted were discarded. Beginning with the most dilute ($1x10^3$ cfu/mL) and continuing through to the least dilute ($1x10^6$ cfu/mL), 100µL of the solution was added to a plate (each dilution to its own plate). The solutions were evenly spread across the plates according to the spread plate method. The plates were inverted and incubated overnight at 37°C. The plates containing between 30 and 300 distinct colonies were counted. The approximate cfu/mL in the original sample ($1x10^9$) was calculated and recorded.

C.) Sample Preparation.

Cream samples AMC-1 and AMC-2 were diluted at 1:1 with sterile Phosphate Buffered Saline (PBS). The volume of cream was calculated by weight (1 gram of cream = 1 mL of cream). 1 gram of cream was weighed into 50 mL sterile centrifuge tubes. The measured cream was not allowed to adhere to sides of tubes. 1 mL of sterile PBS was added to each tube and the tubes were vortexed to homogenize their contents.

D.) Sample Inoculation and Incubation.

The first sample tube was inoculated with 10 µL of the ~$1x10^9$ cfu/mL organism suspension and vortexed. The inoculated tube was incubated at 22 ± 2°C. At 1 minute intervals, the rest of the samples were inoculated in the same way. At the 10 minute incubation mark, 20 mL of SCP neutralizer broth was added to the first tube and vortexed. The neutralizer was added to the rest of the samples in the order that they were inoculated. The test was repeated with a 30 minute incubation period.

E.) Qualitation.

100μL from each original 50 mL centrifuge tube that has been neutralized was removed to a new 50 mL centrifuge tube with 20 mL neutralizer broth and vortexed thoroughly. The centrifuge tubes were incubated at 37°C for 48 hours and observed for turbidity. The tubes were read as + (growth) or - (no growth) and recorded. To eliminate bacteriostasis as a cause of lack of growth, all subcultures were inoculated with < 100 cfu of organism and re-incubated. Growth of these inocula provided sufficient support to eliminate bacteriostasis as a cause of lack of growth.

F.) Quantitation.

Three (3) serial dilutions at 1:10 in SCP neutralizer broth were performed. Beginning with most dilute and continuing through to the least dilute, 100μL of the solution was added to a plate (each dilution to its own plate). The solutions were evenly spread across the plates according to the spread plate method. 100μL from the original neutralized sample tube was directly plated onto TSA. The plates were inverted and placed in a 37°C incubator. They were incubated for 24 hours or until well-defined colonies were seen. Plates containing between 30 and 300 distinct colonies were counted. The approximate cfu/mL in the sample was calculated and recorded.

G.) Pass Criteria.

A sample passed if the colony counts for the Surfacine antimicrobial cream sample showed greater than or equal to a 3 log decrease with respect to the value of the control cream. Results are shown in Table I below.

TABLE I. Initial Efficacy (10 minutes and 30 minutes)

Organism (ATCC#)	Control (Cream Base) Organism, (cfu/mL)		Antimicrobial Cream (AMC) Organism, (cfu/mL)	
	10 min.	30 min.	10 min.	30 min.
Staphylococcus epidermis (12228)	4.4×10^8	4.6×10^8	0	0
Escherichia coli 0157:H7 (43895)	7.3×10^7	7.2×10^7	0	0
Pseudomonas aeruginosa (9027)	3.1×10^8	2.0×10^8	0	0

Example 5

Residual Efficacy of Antimicrobial Hand Cream

Membrane samples treated with Surfacine® Antimicrobial Hand Cream were tested to determine residual efficacy after application. The membranes were tested for activity by incubation of the sample with several robust organisms (i.e., *Staphylococcus epidermis*-ATCC #12228 and *Escherichia coli* 0157:H7-ATCC #43895). If a three log or greater decrease in the number of bacteria was detected as compared to the control, the coated surface was considered to be active.

A.) Making an 18 hour culture.

A well isolated colony from a monoculture grown on Tryptic Soy Agar (TSA) was taken and used to inoculate a 10 mL tube of Tryptic Soy Broth (TSB). The tube was incubated for 18 hours +/- 2 hours, at 37°C (the 18 hour culture should contain ~ 10^9 cfu/mL).

B.) Preparation of Inoculum in PBS.

The culture was centrifuged for 15 minutes at 3400 rpm, and the supernatant was removed and discarded. The pellet was resuspended in 10 mL of PBS, and centrifuged for 15 minutes at 3400 rpm. The supernatant was removed and discarded and the pellet was resuspended in 10 mL PBS. The suspension was then centrifuged for 15 minutes at 3400 rpm. The supernatant was removed and discarded and the pellet was resuspended in 10 mL of PBS.

C.) Dilution of the Inoculum in PBS.

A 1:1000 dilution of the 10^9 cfu/mL solution was performed to get a 10^6 cfu/mL concentration for inoculation.

D.) Dilution of the Inoculum in Tryptic Soy Broth (TSB).

Three (3) 1:10 dilutions in TSB were performed to get a 10^6 cfu/mL concentration.

E.) Counting the Inoculum in PBS or TSB.

A series of four 1:10 dilutions in PBS of the 1 X 10^6 cfu/mL inoculum suspension were carried out as follows:

i) 1:10 → 1mL of $1x10^6$ cfu/mL + 9mL PBS = $1x10^5$ cfu/mL suspension.

ii) 1:10 → 1mL of $1x10^5$ cfu/mL + 9mL PBS = $1x10^4$ cfu/mL suspension.

iii) 1:10 → 1mL of $1x10^4$ cfu/mL + 9mL PBS = $1x10^3$ cfu/mL suspension.

iv) 1:10 → 1mL of $1x10^3$ cfu/mL + 9mL PBS = $1x10^2$ cfu/mL suspension.

Beginning with the most dilute (1x10 $1x10^5$ cfu/mL) and continuing through to the least dilute ($1x10^2$ cfu/mL) a plate was inoculated with 100 µL of each dilution. The solution was evenly spread across the plates according to spread plate method, and the plates were incubated overnight at 37°C. Plates containing between 30 and 300 distinct colonies were counted. The approximate cfu/mL in the original sample ($1x10^6$ cfu/mL) was calculated and recorded.

F.) Membrane Sample Preparation.

A 0.2 micron PS membrane was immersed in either control cream or antimicrobial hand cream (AMC-1), and the excess cream was removed. Membranes were dried in a 37°C oven for 1 hour and then cut into 5/8 inch diameter circles and individually placed in wells of 6-well tissue culture plates.

G.) Inoculation of the Membrane Samples.

The $1x10^6$ cfu/mL suspension of organism was used to inoculate each of the membranes with 100 µL of the suspended organism. The well plate containing the samples was then placed in a humidity chamber and incubated at room temperature for 30 and 60 minutes.

H.) Sampling Membranes.

For each membrane, 2 mL of Neutralizer was put in a 50 mL labeled centrifuge tube. Flamed forceps were used to transfer the membrane to the labeled 50 mL tube, ensuring that the membrane was submerged in the Neutralizer. The tubes were then vortexed thoroughly. A 1:10 dilution series in neutralizer was performed as follows:

a) Aliquot 1 mL of liquid from the 50 mL tube after vortexing and add it to 9 mL Neutralizer

b) Vortex to mix.

c) Take 1 mL of liquid from the 1:10 dilution and add it to 9 mL Neutralizer

d) Vortex to mix.

e) Take 1 mL of liquid from the second 1:10 dilution and add to 9 mL Neutralizer.

f) Vortex to mix.

A TSA plate was labeled for each sample dilution. 100 µL was pipetted onto a separate plate for each dilution tube in a series. Starting with the most dilute, the sample was spread carefully over the agar leaving an even film. A fresh sterile plate spreader was used for each dilution series. The plates were inverted and placed in a 37°C incubator for 24 hours or until well defined colonies were seen.

I.) Counting Plates.

Plates were removed from the incubator after the allotted time. The number of colonies on plates containing between 30 and 300 colonies were counted. The approximate cfu/mL in the original sample was calculated and recorded.

J.) Results.

A sample passed when the count for the sample showed greater than or equal to a 3 log reduction from the value of the control. Results are shown in Table II below.

TABLE II. Residual Efficacy (1 hr. at 37°C) after application

Organism (ATCC#)	Control (Cream Base) Organism, (cfu/mL)		Antimicrobial Cream (AMC) Organism, (cfu/mL)	
	30 min.	60 min.	30 min.	60 min.
Escherichia coli 0157:H7 (43895)	4.5×10^5	3.1×10^5	0	0
Pseudomonas aeruginosa (9027)	8.1×10^4	2.0×10^5	0	0

Example 6:

Alcohol-containing antiseptic hand sanitizer formulation containing self-preserving polymer preservative

The formulation was prepared with Cosmocil CQ™ (PHMB = 20 wt. %) in ethyl alcohol.

Formulation:

Cosmocil CQ™ = 0.5 - 10.0%

Alcohol (denatured, Ethanol 94-96%, Isopropanol = 4-6%) = 70 - 80%

Water =10 – 29.5%

A typical formulation is:

Cosmocil CQ™ = 2.5%

Alcohol (denatured, Ethanol 94-96%, Isopropanol = 4-6%) = 70%

Water = 27.5%

Required amount of water was introduced into alcohol followed by the Cosmocil CQ™ and stirred for 10 minutes. The solution was clear and colorless.

Example 7:

Alcohol-containing antiseptic formulation containing self-preserving polymer preservative with a skin moisturizing thickener

The formulation was prepared with Cosmocil CQ™ in alcohol with Celquat™ SC-230M thickener.

Formulation:

Cosmocil CQ™ = 0.5 - 10%

Alcohol = 70 - 80%

Celquat™ – Thickener = 0.2 - 5%

Water = 5 - 29.3%

A typical formulation is:

Cosmocil CQ™ = 0.5%

Alcohol = 70%

Celquat™ – Thickener = 1%

Water = 28.5%

Required amount of the Celquat™ SC-230 M was sprinkled into water slowly and was allowed to stir overnight at 50° C. Required amount of alcohol was introduced into the water with thickener with stirring, followed by Cosmocil CQ™ in drops. The entire mixture was stirred for 1 more hour. The thickened hand sanitizer is clear and colorless.

Example 8:

Alcohol-containing antiseptic formulation containing self-preserving polymer complexed with silver compound

The formulation was prepared with Cosmocil CQ™ & Ag in alcohol with Celquat™ SC-230M thickener.

Formulation:

Cosmocil CQ™ =0.5 - 10%

AgI = 0.005 – 0.5%

Alcohol = 70 – 80%

Celquat™ – Thickener =0.5 – 5%

Water =4 - 23.0%

Other additives = 0.5 - 6%

A typical formulation consists of:

Cosmocil CQ™ = 2.5%

AgI = 0.05%

Alcohol = 72.6%

Celquat™ – Thickener = 1%

Water = 23.0%

KI = 0.20%

Sodium dodecyl sulfate (SDS) = 0.30%

N-methyl pyrrolidinone (NMP)= 0.35%

Required amount of the Celquat™ SC-230 M was sprinkled into water slowly and was allowed to stir overnight at 50°C. Required amount of alcohol was introduced into the water with thickener with stirring. To the solution containing Cosmocil™, SDS and NMP, the required amount of AgI and KI was introduced and stirred well to get a homogenous mixture. The AgI containing mixture was introduced into the Celquat™ containing aqueous alcohol mixture in drops. The entire mixture was stirred for 1 more hour. The thickened hand sanitizer looks clear and slightly yellow in color.

Example 9:

Iodine-Povidone dermal antiseptic containing antiseptic formulation containing self-preserving polymer complex

The formulation was prepared involving Betadine™, Cosmocil CQ™ (PHMB = 20 wt. %) and Ag. The main ingredient of Betadine™ is Povidone-Iodine, 10 % which is the equivalent of

1% available iodine. Povidone is a 1-Ethenyl-2-pyrrolidinone homopolymer compounded with iodine; polyvinylpyrrolidone-iodine complex. Other inactive ingredients are citric acid, dibasic sodium phosphate, glycerin and others.

Formulation:

Cosmocil CQ™ = 0.5 - 10.0%

AgI = 0.005 – 0.5%

1. Alcohol (denatured, Ethanol 94-96%, Isopropanol = 4-6%) = 10 - 20%

Betadine™ =70 – 90%

Other additives = 0.5 – 6%

Required amount of alcohol was introduced into the Betadine™ solution and mixed well. To the solution containing Cosmocil™, SDS and NMP, the required amount of AgI and KI was introduced and stirred well to get a homogenous mixture. The AgI containing mixture was introduced into the alcohol solution of Betadine™ in drops and mixed well for a period of 30 minutes.

Example 10:

Chlorhexidine dermal antiseptic containing antiseptic formulations containing self-preserving polymer complex

The formulations were prepared using (i) Hibiclens™ and (ii), PHMB-MBDGA adduct complexed with silver. The active ingredient of Hibiclens™ is 4% w/v Hibitane™ (Chlorhexidine gluconate). The active ingredients in Hibistat are 0.5% Chlorhexidine gluconate and 70% isopropanol.

Formulation:

PHMB-MBDGA adduct = 0.5 - 10.0%

Silver compound = 0.005 – 0.5%

Hibiclens™ = 80 - 95%

Required amount of alcohol was introduced into the biguanide-epoxide resin and to the alcoholic solution containing modified biguanide, sodium dodecyl sulfonate (SDS) and N-methyl-2-pyrrolidone (NMP). Silver nitrate and KI were subsequently introduced and stirred well to get a homogenous mixture. The resulting antimicrobial polymer silver complex

solution was introduced dropwise into Hibiclens™ and stirred for a period of 30 minutes. to form a completely miscible solution.

Example 11:

Neutralization of Collagen for in-vitro residual efficacy testing of hand sanitizer formulations

Materials:

Collagen sheets

Phosphate Buffer pH 6.8 2 liters

Procedure:

Collagen sheets were placed in a. 11×13" glass corning dishes and clamped at each corner to prevent the ends from curling up. Preheated phosphate buffer containing $NaBH_4$ was carefully poured over each collagen sheet and gently shaken to saturate the entire sheet. The dishes were placed in a 50°C oven for 10-15 minutes. After reduction, the samples were rinsed with 40-50°C DI H_20 for ~3-5 minutes (static). The above procedure was repeated three times, after which they were hung to dry and packaged appropriately.

Example 12:

Residual Efficacy of Hand Sanitizer formulation on Collagen

The following study was undertaken to characterize the residual antimicrobial efficacy of a Surfacine Hand Sanitizer formulation after product application and subsequent water contact.

Sample Preparation:

Collagen sheets were neutralized according to Example 11. The sheets were cut into squares with length greater than the internal diameter of an open ended x-ray cup with compression rings. Collagen squares were attached to the open ended x-ray cups with compression rings. The formulations were applied on the side with topography consistent with human skin.

Product Application:

The test formulation was applied to the collagen rings with a pipet and spread over the surface to obtain a ratio of (volume of product) to (surface area of collagen) of ~10μL/cm^2 (approximately 70μL per prepared collagen sample cup). The sample was allowed to dry.

Environmental Stress:

To characterize the efficacy of the formulation after a simulated water rinse, collagen rings were contacted with de-ionized water at 40°C maintained at a flow rate to ~1L/minute. for 30 seconds, after which they were air dried.

Inoculation:

An overnight culture of *Pseudomonas aeruginosa* ATCC # 9027 grown in tryptic soy broth (TSB). The culture was adjusted to contain ~10^8 cfu/ml in TSB and 10µL was inoculated onto the center of a collagen sampling ring and was spread with a pipet tip. Samples were incubated at 22 ± 2°C for 1 hour in a humidity chamber maintained at >90% relative humidity. The collagen samples were excised from the rings with a sterile scalpel and transferred with sterile forceps into 10ml of sterile Dey-Engley neutralizing broth (D/E broth) and vortexed. Quantitative assays were performed by preparing 1:10 serial dilutions in phosphate-buffered saline to extinction and 100µL aliquots from the dilution series were transferred and plated by a standard spreading method. Plates were inverted and incubated for 24-48 hours at 37°C or until colonies were visible. Qualitative assays were performed by incubating recovered collagen in 10ml D/E broth for 24-48 hours at 37°C and observing for turbidity.

Persistent antimicrobial activity is characterized in this experiment by a two log reduction in organism viability when compared to the control. As shown in Table 3, addition of a PHMB-MBDGA adduct, formulated with a silver compound, to alcohol-based formulations significantly increases the imparted residual antimicrobial activity of the formulation. This activity persists even after rinsing the surface with water. As shown in Table 4, a PHMB-MBDGA adduct formulated with a silver compound also enhances the residual antimicrobial activity of surgical scrubs, even after subsequent rinsing of the surface. In each case, the PHMB-MBDGA adduct improved the rinsed residual activity by at least two orders of magnitude.

TABLE III. Residual Antimicrobial Efficacy of Hand Sanitizer on Neutralized Collagen After Water Contact Comparison of Alcohol Based Formulations with and without Surfacine

	Log Red. From Control Without Water Contact (Residual) Organisms		Log Red. From Control Following Water Contact (Rinsed Residual) Organisms	
Alcohol Based Formulations	PSA	Ecoli	PSA	Ecoli
Purell (62% EtOH)	0.5	N/T	N/T	N/T
70% EtOH	0 2	N/T	N/T	N/T
70% EtOH w/0 5% Cosmocil CQ	N/T	N/T	1 5	N/T
62% EtOH, 0 25% Cosmocil CQ-MBDGA w/ silver	1 3	N/T	N/T	N/T
70% EtOH, 0 5% Cosmocil CQ-MBDGA w/ silver	2.2	N/T	>1 9	N/T
70% EtOH, 0 5% Cosmocil CQ-MBDGA w/ silver, no thk	4 0	4 5	>1.9	2 5

N/T Not Tested

TABLE IV. Residual Antimicrobial Efficacy of Hand Sanitizer on Neutralized Collagen After Water Contact Comparison of Conventional Scrub Products with and without Surfacine

	Log Red. From Control Without Water Contact (Residual) Organisms		Log Red. From Control Following Water Contact (Rinsed Residual) Organisms	
Conventional Scrub Products	PSA	Ecoli	PSA	Ecoli
Hibistat (70% isopr alc , 0 5% chlorhexidine gluc w/o thickener)	5 0	4 5	N/T	-0 1
Betadine (10% Povidone-Iodine)	N/T	N/T	N/T	1 3
Hibiclens (4.0% chlorhexidine gluconate)	N/T	N/T	N/T	2 9
Conventional Scrub Products + Invention				
Hibistat + 0 5% Cosmocil CQ-MBDGA adduct w/ silver	N/T	N/T	N/T	2 8
Betadine + 0.5% Cosmocil CQ-MBDGA adduct w/ silver	N/T	N/T	N/T	2 4
Hibiclens + 0 5% Cosmocil CQ-MBDGA adduct w/ silver	N/T	N/T	N/T	4 9

N/T Not Tested

Example 13:

Residual efficacy (persistence) provided by Self-Preserving Antimicrobial Polymer (SPAP) in alcohol containing dermal antiseptics

This study was carried out to establish that the *in vitro* antimicrobial studies with collagen sheets accurately reproduce an *in vivo* phenomenon. The experiments were carried out as described for Example 12, except that pigskin or a region of forearm was used in place of the collagen rings where indicated. As shown in Table 5, the residual efficacy of a dermal antiseptic as measured on a region of forearm correlates well with experiments done on collagen rings, and does not correlate as well with experiments done on pigskin.

In Table 5, recovery of control organisms to within 1/2 log is reported as "+++", whereas in an experiment in which only 1-10% of control organisms were recovered is reported as a control organism recovery of "+".

TABLE V. Correlation of *in vitro* substrate to *in vivo* studies.

Study		*Vivo*	*Vitro*	
Substrate		Forearm	Pigskin	Collagen
Incubation Temperature (in degrees Celsius)		~30	30	RT
Control Organism Recovery		+	+++	+++
Sample	**Description**	**Residual**		
Control	No treatment T=0	5.9		6.2
Control	No treatment T=60m	4.7	4.9	6.0
Hibistat™	70% isopropyl alcohol, 0.5% chlorhexidine gluconate, no thickener	1.3	4.4	1.0
5002-74-2	70%EtOH, 0.5% Cosmocil CQ™-MBDGA	3.2	3.6	3.8
5002-75-2	70%EtOH,0.5% Cosmocil CQ™-MBDGA, no thickener	~2.0	4.3	2.0

Average $\log_{10}$ cfu/sample reported.

Example 14:

Demonstration of efficacy of instant invention when used in surgical scrub

The ability of Cosmocil CQ™ or Surfacine® to provide persistent antimicrobial activity was determined using the "Standard Test Method for Evaluation of Surgical Hand Scrub Formulations" described in protocol E 1115-91 of the Annual Book of ASTM Standards, Vol. 11.05, published in September, 1991 by the American Public Health

Association, Inc. of Washington, DC. Participants in the study washed their hands and forearms with the surgical scrub formulation once on days 1 and 5 and three times per day on days 2, 3, and 4. The number of elutable bacteria was determined following the only scrub of days 1 and 5 and following the first scrub of day 2. The number of elutable bacteria was determined both immediately following the scrub and six hours thereafter. At least four subjects were tested at each time point.

As shown in Figure 2, subjects who used a surgical scrub containing Cosmocil CQ™ demonstrated significant antimicrobial activity that persisted even six hours following use of the scrub. The antimicrobial activity was most pronounced after five days of use of the scrub, consistent with the persistent nature of the antimicrobial activity. As shown in Figure 3, subjects who used a surgical scrub containing Surfacine®, formulated as described in Example 1, also demonstrated persistent antimicrobial activity. This activity could be detected for a composition comprising 0.2% Surfacine®, but was more apparent for a composition comprising 0.35% Surfacine® and even more apparent for a composition comprising 0.5% Surfacine®.

Claims:

1. An antimicrobial composition comprising an organic, polycationic, polymeric, antimicrobial material that can bind non-leachably to a surface such that the antimicrobial material does not release biocidal amounts of leachables into a contacting solution.

2. The composition of claim 1, wherein the antimicrobial material comprises a biguanide polymer.

3. The composition of claim 2, wherein the biguanide polymer is poly(hexamethylenebiguanide), poly(hexamethylenebiguanide) hydrochloride, poly(hexamethylenebiguanide) gluconate, poly(hexamethylenebiguanide) stearate, or a derivative thereof.

4. The composition of claim 1, wherein the antimicrobial material is substantially water-insoluble.

5. The composition of claim 2, wherein the biguanide polymer is present as an adduct with a substantially water-insoluble organic compound.

6. The composition of claim 5, wherein the substantially water-insoluble organic compound comprises a reactive member selected from the group consisting of carbodiimide, isocyanate, isothiocyanate, succimidyl ester, epoxide, carboxylic acid, acid chloride, acid halide, acid anhydride, succimidyl ether, aldehyde, ketone, sulfonyl chloride, sulfonyl halide, alkyl methane sulfonate, alkyl trifluoromethane sulfonate, alkyl paratoluene methane sulfonate and alkyl halide.

7. The composition of claim 5, wherein the substantially water-insoluble organic compound is an epoxide selected from the group consisting of methylene-bis-N,N-diglycidylaniline, bisphenol-A-epichlorohydrin and N,N-diglycidyl-4-glycidyloxyaniline.

8. The composition of claim 2, wherein the antimicrobial composition further comprises a metal, and wherein the metal and the antimicrobial material form an antimicrobial complex.

9. The composition of claim 8, wherein the metal renders the antimicrobial material substantially water-insoluble.

10. The composition of claim 8, wherein the metal is silver or a silver compound.

11. The composition of claim 10, wherein the silver compound is silver nitrate.

12. The composition of claim 10, wherein the silver compound is silver iodide.

13. The composition of claim 1, wherein the antimicrobial material can form a covalent bond with the surface.

14. The composition of claim 1, wherein the surface comprises a polypeptide.

15. The composition of claim 14, wherein the polypeptide is collagen.

16. The composition of claim 1, wherein the surface is living tissue.

17. The composition of claim 1, wherein the surface is skin.

18. The composition of claim 13, wherein the surface comprises a polypeptide.

19. The composition of claim 13, wherein the surface comprises a chemical group capable of forming a covalent bond.

20. The composition of claim 19, wherein the covalent bond can be generated at room temperature.

21. The composition of claim 19, wherein the chemical group is selected from the group consisting of an amino group, a carboxylic acid group, a hydroxyl group, or a sulfhydryl group.

22. The composition of claim 19, wherein the chemical group is selected from the group consisting of carbodiimide, isocyanate, isothiocyanate, succimidyl ester, epoxide, carboxylic acid, acid chloride, acid halide, acid anhydride, succimidyl ether, aldehyde,

ketone, sulfonyl chloride, sulfonyl halide, alkyl methane sulfonate, alkyl trifluoromethane sulfonate, alkyl paratoluene methane sulfonate and alkyl halide.

23. The composition of claim 13, wherein the antimicrobial material comprises a chemical group capable of forming a covalent bond.

24. The composition of claim 23, wherein the covalent bond can be generated at room temperature.

25. The composition of claim 23, wherein the chemical group is selected from the group consisting of an amino group, a carboxylic acid group, a hydroxyl group, or a sulfhydryl group.

26. The composition of claim 23, wherein the chemical group is selected from the group consisting of carbodiimide, isocyanate, isothiocyanate, succimidyl ester, epoxide, carboxylic acid, acid chloride, acid halide, acid anhydride, succimidyl ether, aldehyde, ketone, sulfonyl chloride, sulfonyl halide, alkyl methane sulfonate, alkyl trifluoromethane sulfonate, alkyl paratoluene methane sulfonate and alkyl halide.

27. The composition of claim 2, wherein the biguanide polymer is present as an adduct with 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride.

28. The composition of claim 1, wherein the antimicrobial material, when non-leachably bound to a surface, provides an antimicrobial activity that is persistent, even upon repeated contact with an aqueous solution.

29. The composition of claim 1, further comprising a marker.

30. The composition of claim 29, wherein the marker is an optical reporter.

31. The composition of claim 29, wherein the marker comprises a compound detectable under ultraviolet, visible, or infrared irradiation.

32. The composition of claim 31, wherein the marker comprises a compound that fluoresces under ultraviolet or infrared light.

33. The composition of claim 32, wherein the marker is selected from the group consisting of Fluorescent Brightener-28 and Tinopal SFP.

34. The composition of claim 1, further comprising about 30% to about 98% by weight of at least one alcohol selected from the group consisting of ethyl alcohol, n-propanol, and isopropanol.

35. The composition of claim 1, further comprising an antiseptic selected from the group consisting of ethanol, isopropyl alcohol, chlorhexidine gluconate, iodine, iodine-polyvinylpyrrolidone complex, triclosan, triclorocarban, benzalkonium chloride and para-chloro-meta-xylenol.

36. The composition of claim 1, further comprising a thickener, emollient, humectant, skin moisturizing agent or surfactant.

37. A dermal antiseptic composition comprising an organic, polycationic, antimicrobial polymer that binds to skin upon application.

38. The composition of claim 37, wherein the polymer associates with skin through hydrophobic interactions, electrostatic interactions, covalent bonds, or a combination thereof.

39. The composition of claim 37, wherein the antimicrobial polymer comprises poly(hexamethylenebiguanide), poly(hexamethylenebiguanide) hydrochloride, poly(hexamethylenebiguanide) gluconate, poly(hexamethylenebiguanide) stearate, or a derivative thereof.

40. The composition of claim 37, wherein the biguanide polymer is present as an adduct with a substantially water-insoluble organic compound.

41. The composition of claim 40, wherein the substantially water-insoluble organic compound comprises a reactive member selected from the group consisting of carbodiimide, isocyanate, isothiocyanate, succimidyl ester, epoxide, carboxylic acid, acid chloride, acid halide, acid anhydride, succimidyl ether, aldehyde, ketone, sulfonyl chloride, sulfonyl halide, alkyl methane sulfonate, alkyl trifluoromethane sulfonate, alkyl paratoluene methane sulfonate and alkyl halide.

42. The composition of claim 40, wherein the substantially water-insoluble organic compound is an epoxide selected from the group consisting of methylene-bis-N,N-diglycidylaniline, bisphenol-A-epichlorohydrin and N,N-diglycidyl-4-glycidyloxyaniline.

43. The composition of claim 37, wherein the polymer can form a covalent bond with collagen at room temperature.

44. The composition of claim 37, wherein the polymer comprises a chemical group selected from the group consisting of carbodiimide, isocyanate, isothiocyanate, succimidyl ester, epoxide, carboxylic acid, acid chloride, acid halide, acid anhydride, succimidyl ether, aldehyde, amino, hydroxyl, sulfhydryl, ketone, sulfonyl chloride, sulfonyl halide, alkyl methane sulfonate, alkyl trifluoromethane sulfonate, alkyl paratoluene methane sulfonate, and alkyl halide.

45. The composition of claim 37, wherein the polymer forms a self-preserving, antimicrobial barrier upon application to skin, thus imparting a persistent antimicrobial activity.

46. The composition of claim 37, wherein the dermal antiseptic composition comprises a surgical scrub, a pre-operative skin preparation, a healthcare personnel handwash or an antiseptic handwash.

47. The composition of claim 37, wherein the dermal antiseptic composition comprises an antimicrobial soap, antimicrobial cream, antimicrobial hand sanitizer, antimicrobial deodorant or antimicrobial gel.

48. The composition of claim 37, wherein the composition is moisture and sweat resistant.

49. The composition of claim 37, wherein the composition provides deodorizing action over extended periods of time.

50. The composition of claim 37, further comprising an antimicrobial metal.

51. The composition of claim 50, wherein the metal is silver or a silver compound.

52. The composition of claim 51, wherein the silver compound is silver nitrate.

53. The composition of claim 52, wherein the silver compound is silver iodide.

54. The composition of claim 37, wherein the composition comprises an antiseptic selected from the group consisting of ethanol, isopropyl alcohol, chlorhexidine gluconate, iodine, iodine-polyvinylpyrrolidone complex, triclosan, triclorocarban, benzalkonium chloride and para-chloro-meta-xylenol.

55. The composition of claim 37, wherein the composition comprises a thickener, emollient, humectant, skin moisturizing agent or surfactant.

56. The composition of claim 37, further comprising an optical marker detectable under ultraviolet, visible, or infrared irradiation.

57. The composition of claim 56, wherein the marker fluoresces under ultraviolet or infrared light.

58. A method for enhancing the duration of efficacy of a dermal antiseptic formulation, the method comprising the step of:

mixing a polycationic antimicrobial material and a dermal antiseptic formulation, such that the antimicrobial material is capable of forming a self-preserving, antimicrobial barrier upon application of the formulation to skin, thereby enhancing the antimicrobial efficacy of the antiseptic formulation by imparting residual antimicrobial activity.

59. The method of claim 58, wherein the polycationic antimicrobial material comprises a biguanide polymer.

60. The method of claim 59, wherein the biguanide polymer comprises poly(hexamethylenebiguanide), poly(hexamethylenebiguanide) hydrochloride, poly(hexamethylenebiguanide) gluconate, poly(hexamethylenebiguanide) stearate, or a derivative thereof.

61. The method of claim 58, wherein the antimicrobial polycationic material comprises a biguanide polymer and a metal such that the metal is bound to the polycationic material.

62. The method of claim 61, wherein the metal is silver or a silver compound.

63. The method of claim 62, wherein the metal is silver nitrate.

64. The method of claim 63, wherein the metal is silver iodide.

65. The method of claim 59, wherein the biguanide polymer is present as an adduct with a substantially water-insoluble organic compound.

66. The method of claim 65, wherein the substantially water-insoluble organic compound comprises a reactive member selected from the group consisting of carbodiimide, isocyanate, isothiocyanate, succimidyl ester, epoxide, carboxylic acid, acid chloride, acid halide, acid anhydride, succimidyl ether, aldehyde, ketone, sulfonyl chloride, sulfonyl halide, alkyl methane sulfonate, alkyl trifluoromethane sulfonate, alkyl paratoluene methane sulfonate and alkyl halide.

67. The method of claim 65, wherein the substantially water-insoluble organic compound is an epoxide selected from the group consisting of methylene-bis-N,N-diglycidylaniline, bisphenol-A-epichlorohydrin and N,N-diglycidyl-4-glycidyloxyaniline.

68. The method of claim 58, wherein the antimicrobial material comprises a chemical group capable of forming a covalent bond.

69. The method of claim 68, wherein the covalent bond can be generated at room temperature.

70. The method of claim 68, wherein the chemical group is selected from the group consisting of an amino group, a carboxylic acid group, a hydroxyl group, or a sulfhydryl group.

71. The method of claim 68, wherein the chemical group is selected from the group consisting of carbodiimide, isocyanate, isothiocyanate, succimidyl ester, epoxide, carboxylic acid, acid chloride, acid halide, acid anhydride, succimidyl ether, aldehyde, ketone, sulfonyl chloride, sulfonyl halide, alkyl methane sulfonate, alkyl trifluoromethane sulfonate, alkyl paratoluene methane sulfonate and alkyl halide.

72. A method for imparting moisture and sweat resistance to extend the duration of efficacy of a skin deodorant formulation, the method comprising the steps of:

(i) providing a dermal deodorant formulation; and

(ii) mixing a polycationic antimicrobial material in the deodorant formulation, wherein the antimicrobial material can form a moisture and sweat resistant antimicrobial barrier upon application of the formulation to skin, thereby providing deodorizing efficacy over extended periods.

73. The method of claim 72, wherein the polycationic material imparts an antibacterial property to the skin deodorant formulation.

74. The method of claim 72, wherein the polycationic antimicrobial material comprises a biguanide polymer.

75. The method of claim 72, wherein the biguanide polymer comprises poly(hexamethylenebiguanide), poly(hexamethylenebiguanide) hydrochloride, poly(hexamethylenebiguanide) gluconate, poly(hexamethylenebiguanide) stearate, or a derivative thereof.

76. The method of claim 72, wherein the antimicrobial polycationic material comprises a biguanide polymer and a metallic material such that the metallic material is complexed or bound to the polycationic material.

77. The method of claim 76, wherein the metallic material is silver or a silver compound.

78. The method of claim 77, wherein the metallic material is silver nitrate.

79. The method of claim 77, wherein the metallic material is silver iodide.

80. The method of claim 74, wherein the biguanide polymer is present as an adduct with a substantially water-insoluble organic compound.

81. The method of claim 75, wherein the substantially water-insoluble organic compound comprises a reactive member selected from the group consisting of carbodiimide, isocyanate, isothiocyanate, succimidyl ester, epoxide, carboxylic acid, acid chloride, acid halide, acid anhydride, succimidyl ether, aldehyde, ketone, sulfonyl chloride, sulfonyl halide, alkyl methane sulfonate, alkyl trifluoromethane sulfonate, alkyl paratoluene methane sulfonate and alkyl halide.

82. The method of claim 75, wherein the substantially water-insoluble organic compound is an epoxide selected from the group consisting of methylene-bis-N,N-diglycidylaniline, bisphenol-A-epichlorohydrin and N,N-diglycidyl-4-glycidyloxyaniline.

83. The method of claim 72, wherein the antimicrobial material comprises a chemical group capable of forming a covalent bond.

84. The method of claim 83, wherein the covalent bond can be generated at room temperature.

85. The method of claim 83, wherein the chemical group is selected from the group consisting of an amino group, a carboxylic acid group, a hydroxyl group, or a sulfhydryl group.

86. The method of claim 83, wherein the chemical group is selected from the group consisting of carbodiimide, isocyanate, isothiocyanate, succimidyl ester, epoxide, carboxylic acid, acid chloride, acid halide, acid anhydride, succimidyl ether, aldehyde, ketone, sulfonyl chloride, sulfonyl halide, alkyl methane sulfonate, alkyl trifluoromethane sulfonate, alkyl paratoluene methane sulfonate and alkyl halide.

87. A method for detecting the presence of antimicrobial compositions on a surface, the method comprising the steps of:

(i) providing on the surface the antimicrobial composition of claim 29; and

(ii) exposing the surface to a detector capable of detecting the presence of the marker of claim 29 on the surface.

88. A method for monitoring a subject's compliance with aseptic procedures, the method comprising the steps of:

(i) providing to the subject the antimicrobial composition of claim 29; and

(ii) subsequently exposing the subject to a detector capable of detecting the presence of the marker of claim 29 on the subject.

ABSTRACT

TOPICAL ANTIMICROBIAL COMPOSITIONS, METHODS FOR GENERATING SAME, AND MONITORING METHODS UTILIZING SAME

The present invention relates to a topical antimicrobial composition containing an antimicrobial complex that provides sustained antimicrobial disinfecting action upon contact with microorganisms for prolonged periods, without the necessity for reapplication. The topical antimicrobial composition provides both initial and residual contact-killing disinfecting activity, and does not release its antimicrobial components into contacting liquids at levels that result in solution disinfection.

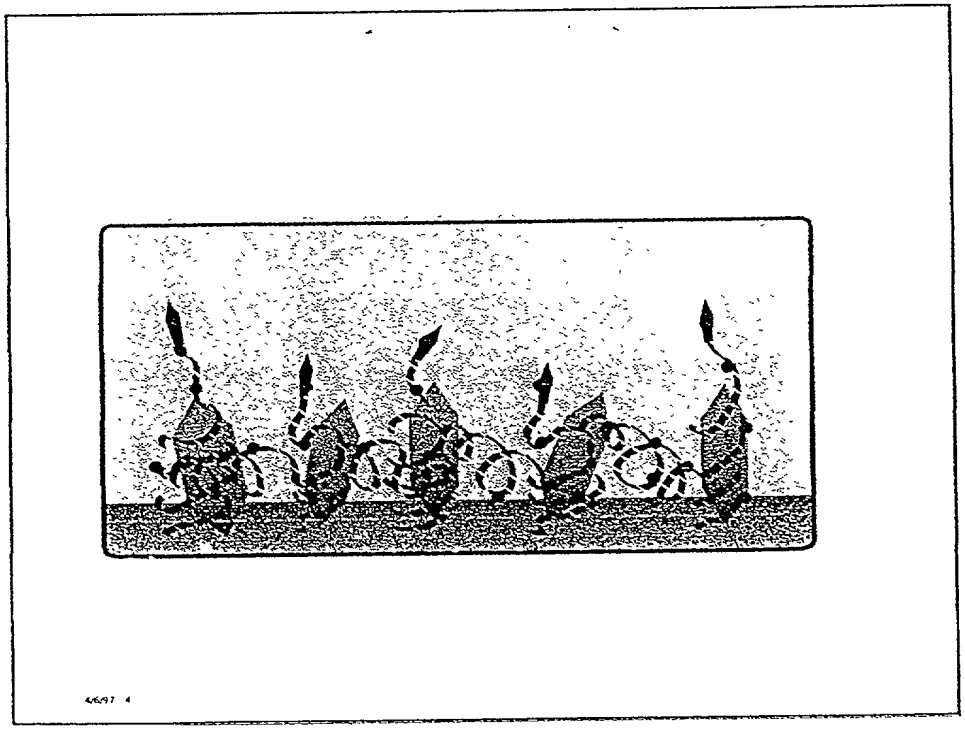


FIG 1A

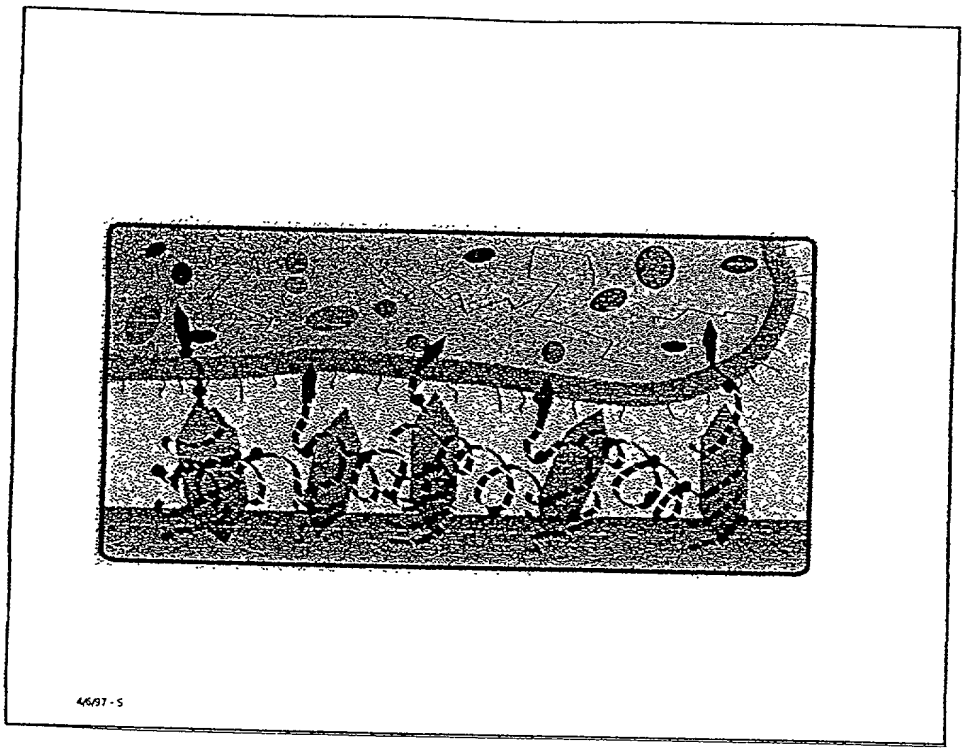


FIG 1B

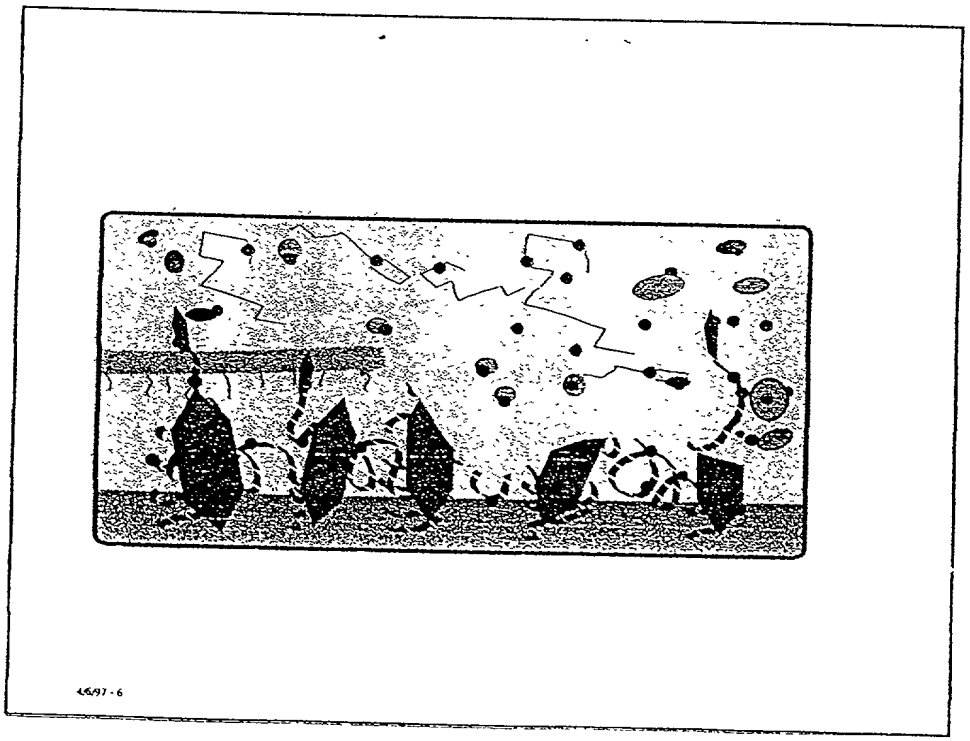
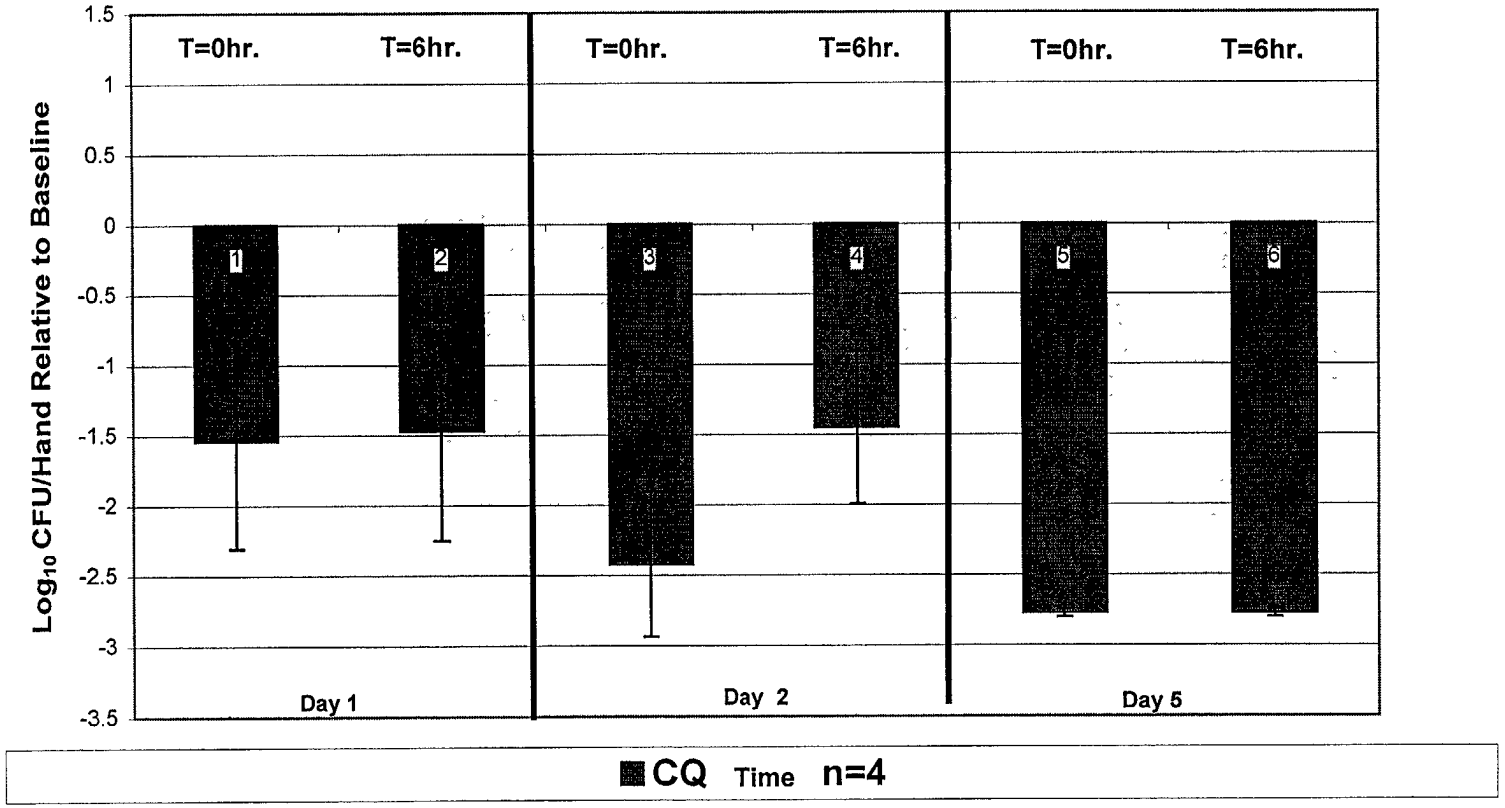


FIG 1C

Figure 2.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-1
-1.5
-2
-2.5
-3
-3.5
Log10 CFU/Hand Relative to Baseline
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T=6hr.
T=0hr.
T=6hr.
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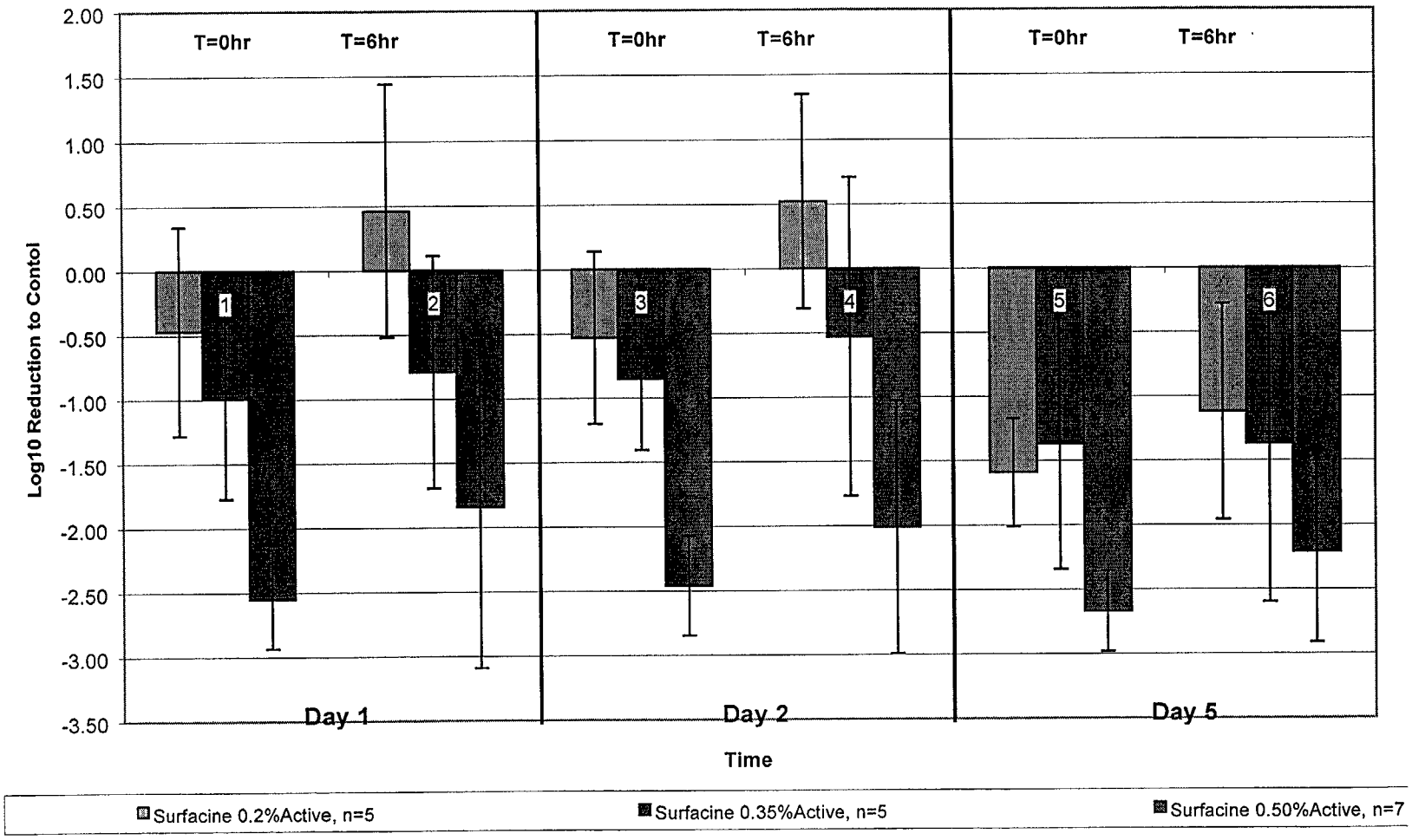
1
2
3
4
5
6
Day 1
Day 2
Day 5
CQ Time n=4

Figure 3.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Log10 Reduction to Contol
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T=6hr
T=0hr
T=6hr
T=0hr
T=6hr
1
2
3
4
5
6
Day 1
Day 2
Day 5
Time
Surfacine 0.2%Active, n=5
Surfacine 0.35%Active, n=5
Surfacine 0.50%Active, n=7